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Dysregulated glucose homeostasis in congenital central hypoventilation syndrome

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Abstract

Background: Congenital central hypoventilation syndrome (CCHS) is a rare disorder of autonomic control. A hypoglycaemic seizure in a 4-year-old girl with CCHS led to a more detailed examination of glycaemic control in a cohort of children with CCHS.

Methods: We conducted an observational cohort study of glucose homeostasis in seven children (3 months to 12 years) with genetically confirmed CCHS using a combination of continuous glucose monitoring (CGM), fasting studies and oral glucose tolerance test (OGTT). CGM was used to compare the effect of diazoxide and dietary intervention in the index patient.

Results: Hypoglycaemia was not elicited by fasting in any of the patients. Increased postprandial glycaemic variability was evident in all patients using CGM, with seven of seven patients demonstrating initial postprandial hyperglycaemia (plasma-glucose concentration >7.8 mmol/L), followed by asymptomatic hypoglycaemia (plasma-glucose concentration ≤2.8 mmol/L) in two of seven patients that was also demonstrated on OGTT. Both diazoxide and low Glycaemic Index (GI) dietary intervention reduced the proportion of CGM readings <4 mmol/L; however, diazoxide also increased the proportion of readings in the hyperglycaemic range.

Conclusions: Glucose variability associated with autonomic dysfunction may be unrecognised in CCHS, particularly in children with more severe phenotypes. This report highlights the occurrence of hyperglycaemia as well as hypoglycaemia in CCHS. Given the challenges of recognising hypoglycaemia based on clinical symptomatology, the use of CGM may facilitate its identification allowing appropriate management. The observed normoglycaemia during fasting combined with increased postprandial plasma blood glucose level (BGL) variability is more consistent with dumping syndrome than persistent hyperinsulinism. Dietary modifications therefore may be more effective than diazoxide in managing hypoglycaemia.

Keywords: congenital central hypoventilation syndrome; diazoxide; hyperglycaemia; hyperinsulinism; hypoglycaemia; seizures.

Introduction

Congenital central hypoventilation syndrome (CCHS) is a rare neurocristopathy resulting from heterozygous polyalanine repeat expansions within the paired-like homeobox 2B (*PHOX2B*) gene [1]. The main symptom is alveolar hypoventilation resulting from an inappropriate central respiratory drive. Patients with the most severe phenotype, which often includes features of autonomic nervous system dysfunction (ANSD) [2], generally have a higher number of polyalanine repeats [3–5].

Dysregulated glucose homeostasis may represent an under-appreciated component of CCHS. Initial case reports described hypoglycaemia occurring in the context of hyperinsulinism [6–11]. A recent study, however, suggested a more complex disorder of glucose regulation, describing hyperglycaemia in both the fasting and postprandial state [12]. Out of 14 patients studied, using 24-h plasma glucose profiles and

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responses to an oral glucose tolerance test (OGTT), 57% were found to have an abnormality of glucose homeostasis. Interestingly, none of the patients exhibited hypoglycaemia after an overnight fast [12]. The results of continuous glucose monitoring (CGM) was first reported in an infant (*PHOX2B* 20/27) with symptomatic postprandial hypoglycaemia [9]. Although hyperglycaemia was not the subject of this paper, the patient's CGM traces demonstrated immediate postprandial glycaemic excursions up to 11.1 mmol/L (200 mg/dL) followed by asymptomatic hypoglycaemia (~2.2 mmol/L) occurring prior to dietary or medical intervention [9]. These findings highlighted the possibility of a dynamic disturbance of glycaemic regulation in CCHS.

The autonomic nervous system (ANS) coordinates the function of pancreatic islets, with parasympathetic activation stimulating both insulin and glucagon secretion, while the sympathetic nervous system inhibits insulin secretion while promoting glucagon release. Disturbances in the oscillatory patterns of insulin secretion have been described in association with diseases affecting the ANS [13]. Abnormal gastrointestinal motility associated with ANSD may also result in altered glucose delivery across the gut thereby contributing to glycaemic variability [14]. Patients with dumping syndrome have early postprandial hyperglycaemia that triggers an exaggerated insulin response resulting in subsequent postprandial hypoglycaemia [14].

The occurrence of an unprovoked, hypoglycaemic seizure occurring 2–3 h following a meal in a 4-year-old girl (PT1) with CCHS prompted a more detailed evaluation of glucose homeostasis in a cohort of seven children with CCHS. We postulated that a disconnect between insulin release and plasma blood glucose level (BGL) secondary to ANSD may contribute to both hyperglycaemia and hypoglycaemia in these patients.

Patients and methods

Subjects

All children with CCHS managed by the respiratory department of the Lady Cilento Children's Hospital, Brisbane, Australia, were invited to participate in a cross-sectional descriptive study. The diagnosis of CCHS was based on the following criteria: (1) persistent central alveolar hypoventilation in the absence of primary lung, neuromuscular, cardiac or brain stem abnormality, (2) absent or weak hypercapnic ventilatory responses and (3) a confirmed genetic diagnosis of CCHS in keeping with the official clinical policy statement of the American Thoracic Society [4]. In total, eight patients with CCHS were screened between 2016 and 2017. One patient (*PHOX2B 20/24*), with significant autistic spectrum disorder but without other ANSD was excluded as they were unable to tolerate CGM. PT1 was diagnosed at 2 months of age while all other patients were diagnosed within the neonatal period upon investigation of hypoventilation. Only PT1 had features of ANSD. Patient characteristics are shown in Table 1.

CGM

Both inpatient and outpatient CGM were undertaken in PT1 and PT2. Outpatient CGM screening was undertaken in PT3 to PT7 for 5 days while children performed their normal daily activities using the Dexcom™ G4 Continuous Glucose Monitoring System (San Diego, CA, USA). Outpatient monitoring was more representative of a daily glycaemic profile and provided the opportunity to monitor patients for a longer period of time. As all children in the study required intensive respiratory support, outpatient monitoring also avoided the practical difficulties associated with extended inpatient monitoring.

None of the children experienced any intercurrent illnesses during their CGM monitoring. Patients were asked to calibrate the CGM measurements at least twice daily, and to validate any hypoglycaemia or hyperglycaemia using glucometer readings (FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System, Abbott Diabetes Care Inc., Alameda, CA, USA). Patients maintained a food diary during the entire period of screening. A single paediatric endocrine dietician provided education and monitoring of all food diaries.

Table 1: Clinical characteristics of participants.

	Age, sex	Genotype[a]	Respiratory support	Cardiac dysautonomia	CNS disorders	GI dysmotility	Neural crest tumours
PT1	4 years, female	20/28	Sleep-Trach	Yes[b]	No	Yes[e]	No
PT2	1 year, female	20/24	Sleep-Trach	No	No	No	No
PT3	10 years, female	20/24	Sleep-NIV	No	No	No	No
PT4	9 years, male	20/24	Sleep-NIV	No	No	No	No
PT5	5 years, male	20/24	Sleep-Trach	No	Yes[c]	No	No
PT6	8 years, female	20/25	Sleep-NIV	No	Yes[c,d]	No	No
PT7	3 month, female	20/24	Sleep-Trach	No	No	No	No

[a]Number of polyalanine repeats. [b]Cardiac pacemaker. [c]Speech delay. [d]Autistic spectrum disorder. [e]Hirschsprung's disease. Trach, tracheostomy; NIV, non-invasive ventilation; GI, gastrointestinal.

Comparison of diazoxide and dietary intervention on glycaemic variability

PT1 had additional CGM to compare the effects of diazoxide treatment and dietary intervention on plasma glucose levels. CGM profiles were obtained for 48 h immediately prior to starting diazoxide, during the last 48 h of a 7-day course of diazoxide treatment (10 mg/kg/day) and for the last 48 h of a dietary intervention that began 8 days after ceasing diazoxide. This dose of diazoxide was chosen because it is commonly used as a starting dose in the treatment of childhood hyperinsulinism and higher doses are associated with the risk of serious adverse effects. The dietary intervention consisted of restricting high Glycaemic Index (GI) carbohydrates (simple sugars) in preference for low GI (complex) carbohydrates only.

Fasting studies

Patients who displayed hypoglycaemia on CGM (PT1 and PT2) underwent an inpatient fasting study (20 h for PT1; 12 h for PT2). The remaining patients had a plasma glucose and insulin measurement after an overnight fast at home.

Oral glucose tolerance test

A standard OGTT was conducted in two patients (PT1 and PT2) who had evidence of hypoglycaemia during CGM screening. This involved ingestion of a glucose solution containing 1.75 g glucose/kg of body weight within 5 min [15]. Blood samples for glucose and insulin were collected at baseline, 30, 60, 90 and 120 min [15].

Definitions

Hypoglycaemia was defined as a plasma glucose concentration of ≤2.8 mmol/L [16] and to be "postprandial" if occurring within 2–4 h after a meal. Postprandial hyperglycaemia was defined as a plasma glucose concentration of >7.8 mmol/L within the first 2 h after a meal [17–20]. Normal glucose tolerance after an OGTT was defined as a plasma glucose concentration of <7.8 mmol/L at 120 min, with glucose intolerance defined as a plasma glucose concentration of 7.8–11.0 mmol/L at 120 min [21].

The study was approved by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC reference number 17/QRCH/233). Informed consent was obtained from parents or legal guardians.

Assays

Insulin was measured by a simultaneous one-step immunoenzymatic assay with limit of detection (LOD) = 0.03 mU/L, and glucose by oxygen rate assay with LOD = 0.2 mmol/L (Beckman Coulter Synchron Clinical Systems, NY, USA).

Results

Spontaneous symptomatic hypoglycaemia

PT1 presented with a spontaneous hypoglycaemic seizure (plasma glucose 2.7 mmol/L) at the age of 4 years, 2–3 h after her typical evening meal. She was not suffering from an intercurrent illness at the time. Urinary ketones were not detected and a robust cortisol response was demonstrated (cortisol 946 mmol/L), but unfortunately information on other counter-regulatory hormones was not available. Intramuscular Glucagon 0.5 mg initially increased her plasma glucose to 3.1 mmol/L but she required an intravenous 10% dextrose bolus (2 mL/kg) followed by a maintenance infusion (4 mg/kg/min glucose infusion rate) for 6 h to maintain normoglycaemia and improve her conscious state. An asymptomatic hypoglycaemic episode (plasma glucose 1.8 mmol/L) requiring oral treatment had occurred during an episode of gastroenteritis 4 months prior but had not been investigated. PT1 also underwent additional inpatient investigations to exclude non-endocrine causes of a seizure, including polysomnography, echocardiography and electroencephalogram. Previous episodes of hypoglycaemia had not been documented in the other patients with CCHS.

Fasting study

PT1 and PT2 demonstrated normal plasma glucose concentrations during fasting studies conducted in the hospital (Table 2) and after an overnight fast prior to an OGTT. The other patients with CCHS also had normal plasma glucose levels after outpatient overnight fasting for at least 12 h (4.1–5.3 mmol/L).

Continuous glucose monitoring

Asymptomatic postprandial hypoglycaemia validated by glucometer readings (2.1 mmol/L and 2.5 mmol/L, respectively) was detected in PT1 and PT2, occurring 2–4 h following typical meals (Table 3, Figure 1). Postprandial hyperglycaemia (8.3–16.7 mmol/L) was also demonstrated 1–2 h following meals in all seven patients, with validation by glucometer testing (Table 3).

Table 2: Summary of findings from fasting study.

	Inpatient formal fasting study				
	Duration	BGL[a] nadir, mmol/L	Final BGL[a], mmol/L	Insulin, mU/L	FFA[b], mmol/L
PT1	20 h	3.0	4.2	1.4	1
PT2	12 h	3.1	3.1	1.3	1.2

[a]BGL, blood glucose level. [b]FFA, free fatty acids (0.1–0.6 mmol/L). Insulin and FFA measured at plasma BGL nadir.

Table 3: Summary of postprandial glucose fluctuations using continuous glucose monitoring (CGM).

	CGM	
	Postprandial glucose[a] peak, mmol/L	Postprandial glucose[b] nadir, mmol/L
PT1	8.3	2.2
PT2	9.3	2.4
PT3	11.1	3.8
PT4	8.4	4.0
PT5	16.7	4.4
PT6	8.0	3.3
PT7	10.3	3.3

[a]Peak levels 1–2 h postprandially. [b]Nadir levels 2–4 h postprandially. Hypoglycaemia = plasma BGL ≤2.8 mmol/L [16]. Hypoglycaemia is recorded to be "postprandial" if occurring within 2–4 h after a meal. Postprandial hyperglycaemia = plasma BGL >7.8 mmol/L within first 2 h after a meal [17–20].

Oral glucose tolerance test

PT1 and PT2 underwent an OGTT that demonstrated asymptomatic non-ketotic hypoglycaemia at 120 min in the presence of detectable insulin levels (Table 4).

Table 4: Oral glucose tolerance test.

	Time, min	BGL[a], mmol/L	Insulin, mU/L	Acylcarnitine profile	BOHB[b], mmol/L	FFA[c], mmol/L
PT 1	0	3.6		Normal		
	60	5.7				
	120	2.2	2.4		0.27	0.57
PT 2	0	5.6		Normal		
	60	10.1				
	120	2.6	1.1		0.11	

[a]BGL, blood glucose level. [b]BOHB, beta hydroxy butyrate (<1.1 mmol/L). [c]FFA, free fatty acids (0.1–0.6 mmol/L). OGTT performed with prescription of 1.75 g of glucose/kg of body weight (maximum of 75 g) consumed <5 min. Normal glucose tolerance = plasma BGL <7.8 mmol/L at 120 min. Glucose intolerance = plasma BGL 7.8–11.0 mmol/L at 120 min [21].

PT2 displayed initial hyperglycaemia (plasma glucose 10.1 mmol/L at 60 min).

Intervention

A low GI dietary intervention was associated with a reduction in the proportion of CGM readings <4 mmol/L when compared with baseline (4% versus 11%), without having an obvious effect on the proportion of CGM readings above 8 mmol/L (4% versus 3%). Diazoxide (10 mg/kg/day) treatment was also associated with a slight reduction in the proportion of CGM readings <4 mmol/L when compared with baseline (9% versus 11%); however, the proportion of CGM readings above 8 mmol/L increased (15% versus 3%) (Table 5, Figure 1).

Discussion

The presented data suggests that postprandial glycaemic variability, particularly hyperglycaemia, is common in CCHS. Hypoglycaemia also occurs, but is less frequent than hyperglycaemia and may be unrecognised in CCHS due to the absence of typical clinical features associated with hypoglycaemia. CGM appears to be more sensitive than formal fasting studies for evaluating hypoglycaemic risk, as the episodes of hypoglycaemia tend to occur after a meal. The postprandial glycaemic fluctuations combined with the absence of fasting induced hypoglycaemia are more consistent with dumping syndrome rather than persistent hyperinsulinism. As such, dietary interventions should be considered as an alternative to diazoxide for the initial management of hypoglycaemia in CCHS.

Meissner et al. first described the occurrence of hypoglycaemia in association with CCHS, with similar cases subsequently reported (Table 6). Episodes of hypoglycaemia often occurred postprandially rather than in response to fasting [8, 9]. In the only other report describing postprandial hyperglycaemia in patients (aged 2 months to 18 years) with CCHS, indices of insulin resistance

Table 5: Continuous glucose monitor metrics.

Plasma blood glucose level	(A) Baseline	(B) Diazoxide	(C) Low GI[a] diet only
Highest value, mmol/L	8.3	11.7	9.7
Lowest value, mmol/L	2.2	2.3	2.2
Period average, mmol/L	4.6	6.2	5.4
Values >7.8 mmol/L	3%	15%	4%
Values 4–8 mmol/L	86%	76%	92%
Values <2.8 mmol/L	11%	9%	4%

[a]GI, Glycaemic Index.

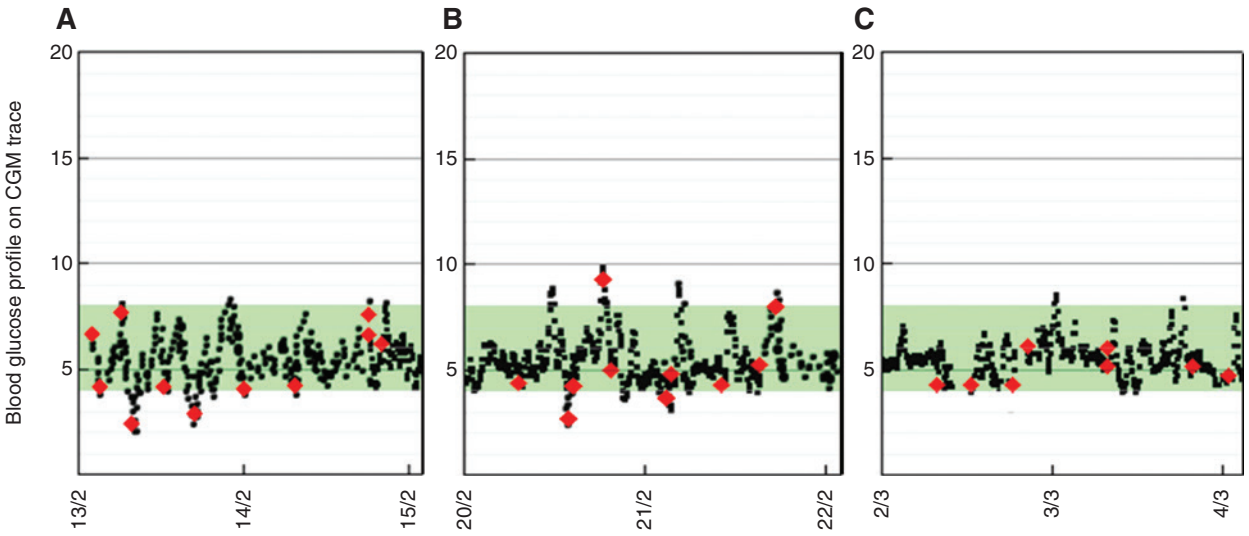

Figure 1: Continuous glucose monitor profile.
Continuous glucose monitoring (CGM) (PT1) over (A) 48 h at baseline, immediately prior to diazoxide. Episodes of postprandial hyperglycaemia followed by asymptomatic hypoglycaemia or trend towards low plasma blood glucose levels (BGLs) were observed following high GI meals in particular. (B) The final 48 h of a 7-day snapshot of diazoxide therapy, demonstrating fewer episodes of postprandial hypoglycaemia during diazoxide therapy, but with a plasma BGL nadir similar to baseline. There was an upward shift in the average plasma BGL and a greater degree of hyperglycaemia. (C) The final 48 h of an 8-day period of dietary intervention only, which allowed for diazoxide "washout" (8 days post diazoxide cessation). A low GI diet provided greater protection against postprandial hypoglycaemic events without increasing the risk of hyperglycaemia, compared to baseline.

and secretion were interestingly normal. In this cohort, hypoglycaemia was not induced by fasting, neither was it detected following an OGTT or after meals [12]. The discrepancy between our findings with regard to postprandial or OGTT-induced hypoglycaemia and those of the previous study may result from a number of factors. Methodological issues with regard to plasma glucose monitoring (CGM versus plasma glucose) or whether the glycaemic response was evaluated after normal meals or during an OGTT need to be considered. In addition, the definitions of "hyperglycaemia" and "hypoglycaemia" may vary slightly between studies. We applied definitions outlined by the International Diabetes Federation Clinical Guidelines Task Force and Lang et al., respectively [16, 20]. Another aspect to consider is the effect of age on the risk of hypoglycaemia, as the natural history may change over time. Our cohort and other cases reported in the literature, are generally younger than those studied by Gelwane et al. who did not report hypoglycaemia [12].

Recognising hypoglycaemia is particularly challenging in children with CCHS, as indicated by the frequency of seizure at first presentation (Table 6). With the exception of the hypoglycaemic seizure in PT1, there was no correlation between symptoms typically ascribed to hypoglycaemia (diaphoresis, pallor and tremor) and low plasma glucose levels in our cohort. Patients with CCHS frequently experience such symptoms at plasma glucose levels >4 mmol/L, which often resolve with increased respiratory support indicating that these symptoms may be attributable to a deterioration in gas exchange from

Table 6: Summary of previous reports.

	Genotype	ANSD	Onset of hypoglycaemia	Symptoms	Fasting hypoglycaemia	Postprandial hypoglycaemia	Plasma BGL nadir, mmol/L	Insulin, mU/L	Ammonia, µmol/L	Urine ketones, g/L	GH, ng/mL	Cortisol, mmol/L	Treatment	Complications of treatment
Meissner et al. [6]	NM	NM	15 months	NM	NM	NM	1.8 (32 mg/dL)	8.5	NM	NM	NM	NM	Diet diazoxide (5 mg/kg/day)	NM
Hennewig et al. [7]	PHOX2B "Missense"	Oesophageal dysmotility	6 weeks	Diaphoresis	NM	NM	0.8 (16 mg/dL)	19.9	NM	NM	NM	NM	Diet diazoxide until 4 months	NM
Farina et al. [7]														
Patient 1	PHOX2B 20/26	NM	13 days	Seizures	NM	NM	0.9 (17 mg/dL)	2.9	92	NM	NM	873 (8 am)	Diet, glucagon, diazoxide (14 mg/kg/day) octreotide (15 µg/kg/day) until 16 months	NM
Patient 2	PHOX2B 20/26	NM	4 months	Seizures	No	Yes	0.6 (11 mg/dL)	37.4	53	NM	1.64	NM	Diet, glucagon diazoxide (10 mg/kg/day) until 22 months	Diazoxide associated hyperglycaemia
Patient 3	PHOX2B 20/26	NM	9 months	Seizures	NM	Yes	2.0 (36 mg/dL)	19.2	48	0.2	1.28	873 (8 am)	Diet, Diazoxide (10 mg/kg/day)	NM
Marics et al. [9]	PHOX2B 20/27	NM	14 days	NM	NM	Yes	2.6 (48 mg/dL)	43	NM	NM	NM	NM	No response to diet or hydrocortisone diazoxide (6–10 mg/kg/day)	NM
Ganti et al. [11]	PHOX2B 20/26	NM	7 months	Seizures	NM	NM	2.5 (46 mg/dL)	3.0	NM	<0.1	NM	470	Diazoxide 7.5 mg/kg/day	NM
Hopkins et al. [10]	PHOX2B 20/27	Hirschsprung's disease	5 months	Seizures	NM	NM	1.6 (30 mg/dL)	NM	NM	NM	NM	NM	Diet diazoxide (10 mg/kg/day)	Diazoxide associated hyperglycaemia

NM, not measured; ANSD, autonomic nervous system dysfunction; BGL, blood glucose level; GH, growth hormone.

under-ventilation. This highlights the importance of having a sensitive screening strategy for detecting hypoglycaemic risk, such as CGM. It would appear from the current findings and previous studies that formal fasting is unlikely to be useful in identifying patients at risk of hypoglycaemia. It is unclear whether unrecognised hypoglycaemia contributes to reduced neurocognitive performance in CCHS but the available evidence highlights the need to develop a screening strategy aimed at identifying hypoglycaemic risk in these children. Patients with glycaemic disturbance reported thus far harbour six or more alanine repeat expansions. Given that there is a genotype-phenotype correlation observed in other features of CCHS, the severity of glycaemic dysregulation may also be anticipated by the genotype. The limited evidence thus far supports initially screening the high-risk group, defined according to age (<3 years), polyalanine repeat length (≥27 repeats) and the presence of ANSD [4]. CGM is likely to be more sensitive in detecting hypoglycaemia than formal fasting studies in CCHS, with its utility demonstrated in other disorders which result in similar postprandial glucose excursions [22].

Hypoglycaemia in CCHS has been ascribed to hyperinsulinism and therapeutic strategies have included dietary interventions and medications aimed at reducing insulin release (Tables 4 and 6). Diazoxide treatment in our patient was associated with a decrease in the proportion of hypoglycaemic readings. However, the mean plasma glucose concentration and the proportion of hyperglycaemic readings were increased, similar to previous reports (Table 6). Compared to diazoxide, the dietary intervention achieved a greater reduction in glucose readings less than 4 mmol/L, while at the same time increasing the proportion of readings in the target range. Previous studies have also reported improved hypoglycaemia with dietary interventions in all but one case [9]. Given that diazoxide treatment is associated with a range of other side-effects in addition to hyperglycaemia [23, 24], it would seem reasonable to consider a dietary intervention as a first step before commencing diazoxide.

While the mechanisms underlying glycaemic dysregulation in CCHS are not well understood, the initial hyperglycaemia followed by hypoglycaemia after a meal indicates a temporal disconnection between the plasma glucose level and the insulin response. The complex neural and humoral control of glucose homeostasis, and the central role that *PHOX2B* plays in the ANS, raises the possibility that there are multiple defects in glycaemic control in CCHS. The inappropriately normal or frankly elevated insulin level at the time of hypoglycaemia may represent an imbalance between the inhibitory action of the sympathetic system and the stimulatory action of the parasympathetic system. Dysregulated insulin secretion has also been reported in other conditions with ANSD, such as dopamine beta-hydroxylase (DBH) deficiency. DBH null ($DBH^{-/-}$) mice experience hyperinsulinaemia associated with loss of inhibitory sympathetic tone combined with increased parasympathetic tone [25]. Although DBH-deficient humans also have episodic hypoglycaemia, it is not yet clear if this is related to hyperinsulinaemia [26]. Interestingly, *PHOX2B* is an important regulator of DBH, and *PHOX2B* mutations lead to impaired transactivation of the DBH promoter [27]. A rapid delivery of glucose across the gastrointestinal tract may also be contributing to the postprandial glycaemic variability in CCHS. Dumping syndrome describes the rapid absorption of carbohydrate after a meal resulting in early hyperglycaemia, followed by an exaggerated glucagon-like peptide-1 (GLP-1) dependent insulin surge [28, 29]. Abnormal glucose homeostasis related to gut dysfunction has been described in a case series of children with dumping syndrome, including one child with CCHS, Hirschsprung's disease and generalised ANSD [14]. Hormonal analyses showed an exaggerated release of insulin resulting in a rapid fall in glucose. An inadequate glucagon response may also contribute to the persistence of hypoglycaemia after the decline in circulating insulin to undetectable levels. GLP-1 is defined as an "incretin" based on its ability to enhance glucose-induced insulin secretion in response to a meal [30–32], and has other actions that complement the incretin effect, including inhibition of glucagon secretion [33]. GLP-1 receptor blockers have been shown to reduce insulin secretion [28, 34, 35] and prevent hypoglycaemia in patients suffering from postprandial hypoglycaemia following gastric bypass surgery. The ANSD seen in CCHS could be influencing both glucose delivery (gut function) and glucose disposal (insulin secretion). It would be of interest to compare glycaemic variability after an intravenous versus an oral glucose load, and to measure postprandial GLP-1 levels in children with CCHS.

The current study is subject to some limitations given the relatively small sample size, with the majority of patients having mild *PHOX2B* mutations. Within our cohort, we observed that glycaemic dysregulation was most profound in the patient (PT1) with the highest number of polyalanine repeat expansions, and the most severe phenotype that included ANSD. Given that five of seven patients had an identical and relatively mild genotype (*PHOX2B* 20/24), our study was not able to examine whether there is a genotype-phenotype correlation with regard to glycaemic variability. Additionally, our patient's medical and psychosocial needs posed challenges with

regard to undertaking more detailed metabolic assessments, including continuous inpatient blood glucose measurements. The comparison between the effects of diazoxide treatment and dietary intervention on glycaemic variability was also only assessed in one patient and requires further evaluation in a larger cohort with detailed recording of dietary intake. Finally, although CGM provides potential benefits relative to episodic plasma glucose measurements in detecting dynamic glucose profiles, it is still a maturing technology [36].

Conclusions

Glucose variability may be unrecognised in CCHS, particularly in children with features of ANSD. This report highlights the occurrence of hyperglycaemia as well as hypoglycaemia in CCHS. Given the challenges of recognising hypoglycaemia based on clinical symptomatology, and the fact that it commonly occurs post-prandially, CGM may be a useful strategy to screen for hypoglycaemia. The observed normoglycaemia during fasting with increased postprandial plasma glucose variability is consistent with a dynamic abnormality in glucose control rather than persistent hyperinsulinism. ANSD is likely to be impairing the responses that normally co-ordinate glucose delivery across the gut and peripheral insulin mediated glucose disposal. Therefore, dietary modifications may be more effective than diazoxide in managing hypoglycaemia. The long-term consequences and the natural history of dysregulated glucose homeostasis in CCHS are unknown.

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